

Day : Thursday
Date: 11/9/2006
Time: 20:12:44

PALM INTRANET**Inventor Information for 10/813760**

Inventor Name	City	State/Country
BERNSTEIN, JOEL E.	DEERFIELD	ILLINOIS

[Appn Info](#) [Contents](#) [Petition Info](#) [Atty/Agent Info](#) [Continuity/Reexam](#) [Foreign Data](#) [Inventor](#)

Search Another: Application# or Patent#

PCT / / or PG PUBS #

Attorney Docket #

Bar Code #

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L2 ANSWER 39091 OF 39092 REGISTRY COPYRIGHT 2006 ACS on STN

RN 63-68-3 REGISTRY

ED Entered STN: 16 Nov 1984

CN L-Methionine (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Methionine, L- (8CI)

OTHER NAMES:

CN (S)-2-Amino-4-(methylthio)butanoic acid

CN α -Amino- γ -methylmercaptobutyric acid

CN γ -Methylthio- α -aminobutyric acid

CN 1139: PN: WO2004048938 SEQID: 1139 claimed protein

CN 2-Amino-4-(methylthio)butyric acid

CN 395: PN: US20030049618 SEQID: 395 claimed protein

CN 395: PN: US20060084082 SEQID: 395 claimed protein

CN 46: PN: WO2004076659 FIGURE: 7 claimed protein

CN Acimethin

CN Butanoic acid, 2-amino-4-(methylthio)-, (S)-

CN Cymethion

CN h-Met-oh

CN L-(-)-Methionine

CN L- α -Amino- γ -methylthiobutyric acid

CN L-Homocysteine, S-methyl-

CN L-Methionine

CN Methionine

CN NSC 22946

CN S-Methionine

CN S-Methyl-L-homocysteine

CN Secretory peptide (human clone HTXDU73)

FS STEREOSEARCH

DR 7005-18-7, 24425-78-3

MF C5 H11 N O2 S

CI COM

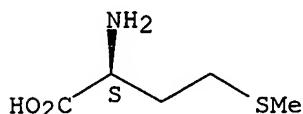
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PATDPASPC, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB

(*File contains numerically searchable property data)

Other Sources: DSL**, EINECS**, TSCA**

(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

39048 REFERENCES IN FILE CA (1907 TO DATE)

957 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

39135 REFERENCES IN FILE CAPLUS (1907 TO DATE)

10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L2 ANSWER 39092 OF 39092 REGISTRY COPYRIGHT 2006 ACS on STN

RN 59-51-8 REGISTRY

ED Entered STN: 16 Nov 1984

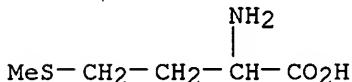
CN Methionine (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN DL-Methionine
CN Methionine, DL- (8CI)

OTHER NAMES:

CN (±)-Methionine
CN α-Amino-γ-methylmercaptobutyric acid
CN Acimetion
CN Amurex
CN Banthionine
CN Cynaron
CN DL-2-Amino-4-(methylthio)butyric acid
CN Dyprin
CN Lactet
CN Lobamine
CN Meonine
CN Meprom M 85
CN Methilanin
CN Metione
CN Neston
CN NSC 9241
CN Pedameth
CN Racemethionine
CN Rhodimet NP 99
CN Urimeth
MF C5 H11 N O2 S
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS,
BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX,
CHEMLIST, CIN, CSCHEM, CSNB, DETHERM*, EMBASE, GMELIN*, HSDB*, IFICDB,
IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PIRA, PROMT,
RTECS*, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

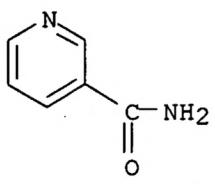


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3215 REFERENCES IN FILE CA (1907 TO DATE)
81 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3221 REFERENCES IN FILE CAPLUS (1907 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L3 ANSWER 37730 OF 37738 REGISTRY COPYRIGHT 2006 ACS on STN
RN 98-92-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Nicotinamide (8CI)
OTHER NAMES:
CN β -Pyridinecarboxamide
CN 3-(Aminocarbonyl)pyridine
CN 3-Amidopyridine
CN 3-Carbamoylpyridine
CN 3-Pyridinecarboxylic acid amide
CN Aminicotin
CN Benicot
CN Delonin Amide
CN Dipegyl
CN m-(Aminocarbonyl)pyridine
CN NAM
CN Niacinamide
CN Niavit PP
CN Nicamina
CN Nicamindon
CN Nicasir
CN Nicobion
CN Nicofort
CN Nicosan 2
CN Nicosylamide
CN Nicotilamide
CN Nicotine acid amide
CN Nicotinic acid amide
CN Nicotinic amide
CN Nicotylamide
CN Nicovit
CN Nicovitina
CN Nictoamide
CN Niocinamide
CN Niozymin
CN NSC 13128
CN NSC 27452
CN Papulex
CN Pelmin
CN Pelmine
CN Pelonin amide
CN Vi-Nicotyl
CN Vitamin B
CN Vitamin B3
DR 123574-63-0, 37321-14-5, 78731-47-2
MF C6 H6 N2 O
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*,
BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS,
CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU,
EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*,
MSDS-OHS, NAPRALERT, PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER,
USAN, USPAT2, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



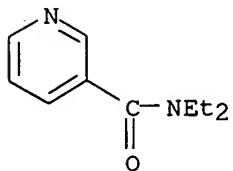
L3 ANSWER 37734 OF 37738 REGISTRY COPYRIGHT 2006 ACS on STN
RN 59-26-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN 3-Pyridinecarboxamide, N,N-diethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Nicotinamide, N,N-diethyl- (8CI)
OTHER NAMES:
CN 3-(N,N-Diethylcarbamoyl)pyridine
CN Anacardone
CN Anacordone
CN Astrocar
CN Canfodiamina
CN Carbamidal
CN Cardamine
CN Cardiamid
CN Cardiamide
CN Cardiamine
CN Cardimon
CN Coracon
CN Coractiv N
CN Coramine
CN Coramine (pharmaceutical)
CN Cordiamin
CN Cordiamine
CN Corediol
CN Cormed
CN Cormid
CN Cormotyl
CN Cornotone
CN Corvin
CN Corvitol
CN Corvotone
CN Diethylnicotinamide
CN Dynacoryl
CN Ecoran
CN Eucoran
CN Kordiamin
CN N,N-Diethyl-3-pyridinecarboxamide
CN N,N-Diethylnicotinamide
CN Ni-Cor
CN Niamine
CN Nicamide
CN Nicetamide
CN Nicethamide
CN Nicotine
CN Nicotinic acid diethylamide
CN Nikardin
CN Niketamide
CN Niketamine
CN Nikethamide
CN Niketharol
CN Nikethyl
CN Nikorin
CN Niquetamide
CN NSC 130820
CN NSC 169863
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for
DISPLAY
MF C10 H14 N2 O
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD,
CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU,

EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE,
MRCK*, PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2,
USPATFULL

(*File contains numerically searchable property data)

Other Sources: EINECS**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1237 REFERENCES IN FILE CA (1907 TO DATE)

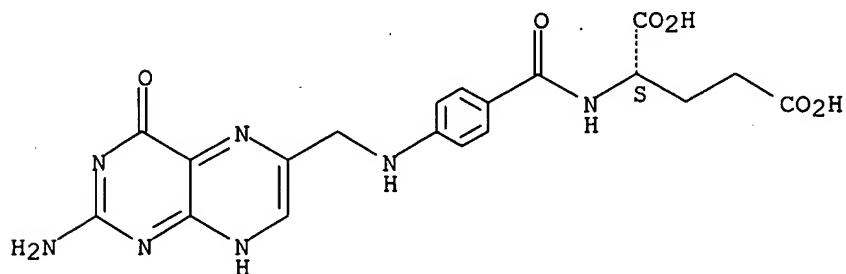
34 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

1237 REFERENCES IN FILE CAPLUS (1907 TO DATE)

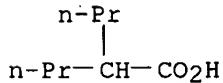
25 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L4 ANSWER 211 OF 214 REGISTRY COPYRIGHT 2006 ACS on STN
 RN 59-30-3 REGISTRY
 ED Entered STN: 16 Nov 1984
 CN L-Glutamic acid, N-[4-[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Folic acid (8CI)
 OTHER NAMES:
 CN Acifolic
 CN Cytofol
 CN Dosfolat B activ
 CN Folacid
 CN Folacin
 CN Folbal
 CN Folcidin
 CN Foldine
 CN Folettes
 CN Foliamin
 CN Folicet
 CN Folipac
 CN Folsan
 CN Folsaure
 CN Folsav
 CN Folvite
 CN Incafolic
 CN Liver Lactobacillus casei factor
 CN Millafol
 CN NSC 3073
 CN PGA
 CN Pterooyl-L-glutamic acid
 CN Pterooyl-L-monoglutamic acid
 CN Pterooylglutamic acid
 CN Pterooylmonoglutamic acid
 CN Vitamin Bc
 CN Vitamin Be
 CN Vitamin M
 FS STEREOSEARCH
 DR 33609-88-0
 MF C19 H19 N7 O6
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO,
 CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN,
 CSCHEM, CSNB, DDFU, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT,
 IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PIRA,
 PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
 (*File contains numerically searchable property data)
 Other Sources: DSL**, EINECS**, TSCA**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



L20 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2006 ACS on STN
RN 99-66-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN Pentanoic acid, 2-propyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Valeric acid, 2-propyl- (6CI, 7CI, 8CI)
OTHER NAMES:
CN 2-Propylpentanoic acid
CN 2-Propylvaleric acid
CN 4-Heptanecarboxylic acid
CN 44089
CN Acetic acid, dipropyl-
CN Depakine
CN Dipropylacetic acid
CN DPA
CN Erogenyl
CN Mylproin
CN n-Dipropylacetic acid
CN NSC 93819
CN **Valproic acid**
MF C8 H16 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

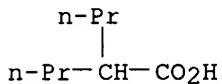


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4429 REFERENCES IN FILE CA (1907 TO DATE)
158 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4445 REFERENCES IN FILE CAPLUS (1907 TO DATE)
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L19 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 76584-70-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN Pentanoic acid, 2-propyl-, sodium salt (2:1) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Abbott 50711
CN Depakote
CN Divalproex sodium
CN Epival
CN Sodium hydrogen bis(2-propylpentanoate)
CN Sodium hydrogen bis(2-propylvalerate)
CN Sodium hydrogen divalproate
CN Valdisoval
CN Valproate semisodium
AR 133299-66-8
MF C8 H16 O2 . 1/2 Na
CI COM
LC STN Files: ADISNEWS, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS,
CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE,
GMELIN*, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*,
PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2,
USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO
CRN (99-66-1)



● 1/2 Na

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

287 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
289 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

L16 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2006 ACS on STN
RN 86386-73-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1H-1,2,4-Triazole-1-ethanol, α -(2,4-difluorophenyl)- α -(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN Biozolene
CN Diflucan
CN Elazor
CN Fluconazole

CN Flucostat

CN Flumycon

CN Flunazol

CN Flusol

CN Fluzon

CN Triflucan

CN UK 49858

CN Zoltec

DR 123631-92-5

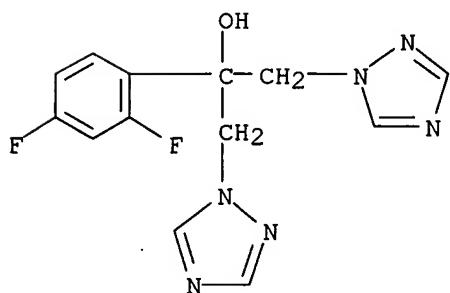
MF C13 H12 F2 N6 O

CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, IFICDB, IFIUDB, IMSCOSEARCH, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU

(*File contains numerically searchable property data)

Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3130 REFERENCES IN FILE CA (1907 TO DATE)

30 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

3146 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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L15 ANSWER 23 OF 23 REGISTRY COPYRIGHT 2006 ACS on STN

RN 59-67-6 REGISTRY

ED Entered STN: 16 Nov 1984

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Nicotinic acid (7CI, 8CI)

OTHER NAMES:

CN β -Pyridinecarboxylic acid

CN 3-Carboxylpyridine

CN 3-Carboxypyridine

CN 3-Pyridylcarboxylic acid

CN Akotin

CN Apelagrin

CN Daskil

CN E 375

CN Efacin

CN Enduracin

CN Linic

CN Niac

CN **Niacin**

CN Niacor

CN Niaspan

CN Nicacid

CN Nicangin

CN Nico-Span

CN Nicobid

CN Nicodelmine

CN Nicolar

CN Niconacid

CN Nicosan 3

CN Nicotinipca

CN Nicyl

CN NSC 169454

CN Nyclin

CN Pellagrin

CN Pelonin

CN **Slo-niacin**

CN SR 4390

CN Vitamin B5

CN Wampocap

DR 123574-58-3

MF C6 H5 N O2

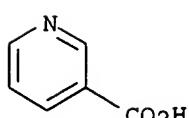
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LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABAB, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB

(*File contains numerically searchable property data)

Other Sources: DSL**, EINECS**, TSCA**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)



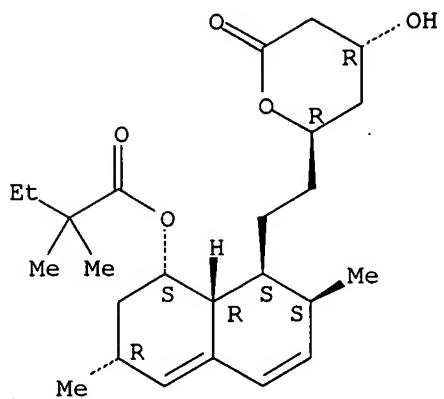
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

16810 REFERENCES IN FILE CA (1907 TO DATE)
786 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
16861 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L14 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2006 ACS on STN
RN 79902-63-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8a β]]-
OTHER NAMES:
CN (+)-Simvastatin
CN Cholestat
CN Denan
CN Eucor
CN Kolestevan
CN L 644128-000U
CN Lipex
CN Lipinorm
CN Liponorm
CN Lipovas
CN Lodales
CN MK 733
CN Modutrol
CN Nor-Vastina
CN Rechol
CN Simcor
CN Simovil
CN Simvastatin
CN Simvastatin lactone
CN Simvotin
CN Sinvacor
CN Sinvascor
CN Sivastin
CN Statin
CN Synvinolin
CN Valemia
CN Velostatin
CN Zocor
CN Zocord
FS STEREOSEARCH
DR 98609-43-9, 118607-03-7
MF C25 H38 O5
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NAPRALERT, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3298 REFERENCES IN FILE CA (1907 TO DATE)

79 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

3317 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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L13 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2006 ACS on STN

RN 134523-00-5 REGISTRY

ED Entered STN: 28 Jun 1991

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (β R, δ R)-(9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, [R-(R*,R*)]-

OTHER NAMES:

CN (β R, δ R)-2-(p-Fluorophenyl)- β,δ -dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid

CN (3R,5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpiperidin-1-yl]-3,5-dihydroxyheptanoic acid

CN Atorvastatin

CN Atorvastatin acid

CN Cardyl

FS STEREOSEARCH

MF C33 H35 F N2 O5

CI COM

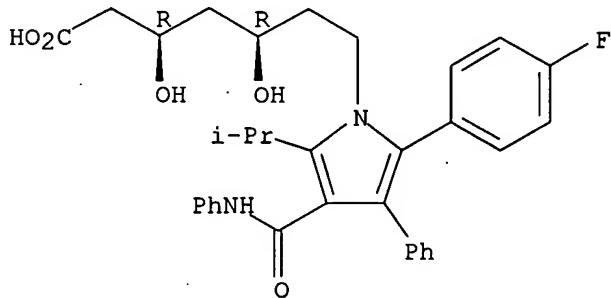
SR CA

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DRUGU, EMBASE, HSDB*, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Other Sources: WHO

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2274 REFERENCES IN FILE CA (1907 TO DATE)

54 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

2287 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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L13 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2006 ACS on STN

RN 134523-01-6 REGISTRY

ED Entered STN: 28 Jun 1991

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, monosodium salt, (β R, δ R)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, monosodium salt, [R -(R^* , R^*)]-

OTHER NAMES:

CN Atorvastatin sodium

FS STEREOSEARCH

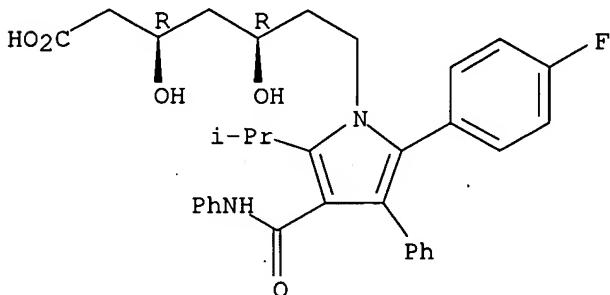
MF C33 H35 F N2 O5 . Na

SR CA

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, IMSPATENTS, IMSRESEARCH, MRCK*, USPAT2, USPATFULL
(*File contains numerically searchable property data)

CRN (134523-00-5)

Absolute stereochemistry.



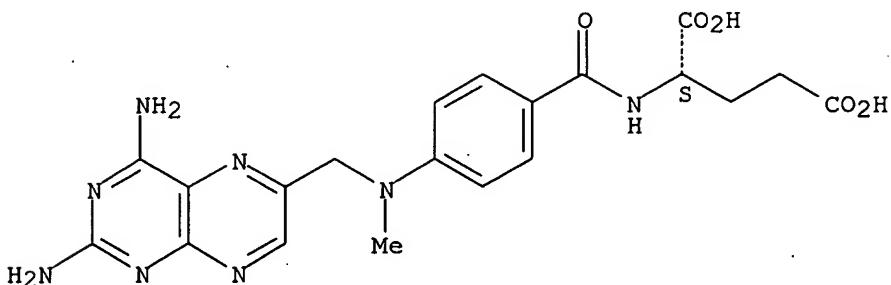
21 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

22 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L11 ANSWER 102 OF 102 REGISTRY COPYRIGHT 2006 ACS on STN
 RN 59-05-2 REGISTRY
 ED Entered STN: 16 Nov 1984
 CN L-Glutamic acid, N-[4-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzo
 y1]- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Glutamic acid, N-[p-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl
]-, L-(+)- (8CI)
 OTHER NAMES:
 CN (+)-Amethopterin
 CN 4-Amino-10-methylfolic acid
 CN 4-Amino-N10-methylfolic acid
 CN 4-Amino-N10-methylpteroylglutamic acid
 CN Amethopterin
 CN Amethopterine
 CN Antifolan
 CN CL 14377
 CN EMT 25299
 CN Emtexate
 CN L-Amethopterin
 CN L-Methotrexate
 CN Ledertrexate
 CN Metatrexan
 CN Methotrexat-Ebewe
 CN Methotrexate
 CN Methylaminopterin
 CN Mexate
 CN MTX
 CN N-[p-[(2,4-Diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-(+)-glutamic
 acid
 CN NSC 740
 CN R 9985
 CN Rheumatrex
 FS STEREOSEARCH
 MF C20 H22 N8 O5
 CI COM
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS,
 BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST,
 CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB,
 IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PROMT, PROUSDDR, PS,
 RTECS*, SCISEARCH, SPECINFO, TOXCENTER, UOLIDAT, USAN, USPAT2, USPATFULL,
 VETU
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, NDSSL**, TSCA**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13482 REFERENCES IN FILE CA (1907 TO DATE)

846 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

13538 REFERENCES IN FILE CAPLUS (1907 TO DATE)

73 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L10 ANSWER 132 OF 132 REGISTRY COPYRIGHT 2006 ACS on STN

RN 103-90-2 REGISTRY

ED Entered STN: 16 Nov 1984

CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Acetanilide, 4'-hydroxy- (7CI, 8CI)

OTHER NAMES:

CN 4'-Hydroxyacetanilide

CN 4-(Acetylamino)phenol

CN 4-(N-Acetylamino)phenol

CN 4-Aacetamidophenol

CN **4-Aacetaminophenol**

CN 4-Hydroxyacetanilide

CN Abensanil

CN Acamol

CN Acenol

CN Acenol (pharmaceutical)

CN Acetagesic

CN Acetalgin

CN Acetaminofen

CN **Acetaminophen**

CN Algotropyl

CN Alpiny

CN Alvedon

CN Amadil

CN Anaflon

CN Anelix

CN Anhiba

CN Apamid

CN Apamide

CN APAP

CN Banesin

CN Ben-u-ron

CN Benzenediol, 4-amino-, 2(or 3)-acetate

CN Bickie-mol

CN Biocetamol

CN Calpol

CN Captin

CN Cetadol

CN Citramon P

CN Claratal

CN Clixodyne

CN Crocin

CN Dafalgan

CN Daphalgan

CN Datril

CN Dial-a-gesic

CN Dirox

CN Disprol

CN Doliprane

CN Dolprone

CN Duorol

CN Dymadon

CN Efferalgan

CN Endophy

CN Enelfa

ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for

DISPLAY

DR 719293-04-6, 8055-08-1

MF C8 H9 N O2

CI COM

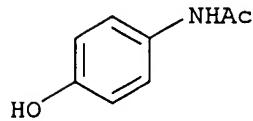
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS,

BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS,
CHEMINFORMRX, CHEMLIST, CIN, CSHEM, CSNB, DDFU, DETHERM*, DRUGU,
EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*,
MSDS-OHS, PATDPASPC, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SPECINFO,
SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU

(*File contains numerically searchable property data)

Other Sources: DSL**, EINECS**, TSCA**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

12807 REFERENCES IN FILE CA (1907 TO DATE)

280 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

12858 REFERENCES IN FILE CAPLUS (1907 TO DATE)

2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

(FILE 'HOME' ENTERED AT 20:18:26 ON 09 NOV 2006)

FILE 'REGISTRY' ENTERED AT 20:18:38 ON 09 NOV 2006

FILE 'REGISTRY' ENTERED AT 20:18:54 ON 09 NOV 2006

L1 0 S FLUCANOZOLE
L2 39092 S METHIONINE
L3 37738 S NICOTINAMIDE
L4 214 S FOLIC ACID

FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 20:25:47 ON 09 NOV 2006

L5 225232 S 63-68-3/RN OR 59-51-8/RN OR METHIONINE
L6 149134 S 98-92-0/RN OR NICOTINAMIDE OR VITAMIN B OR NIACINAMIDE OR NIC
L7 74827 S 59-30-3/RN OR FOLIC ACID OR PTEROYLGUTAMIC ACID OR PTEROYLMO
L8 4350 S L5 AND L6
L9 1461 S L8 AND L7

FILE 'REGISTRY' ENTERED AT 20:28:57 ON 09 NOV 2006

L10 132 S ACETAMINOPHEN
L11 102 S METHOTREXATE
L12 0 S ATROVASTATIN
L13 12 S ATORVASTATIN
L14 17 S SIMVASTATIN
L15 23 S NIACIN
L16 4 S FLUCONAZOLE

FILE 'REGISTRY' ENTERED AT 20:31:22 ON 09 NOV 2006

SET TERMSET E#
DEL SEL Y
SEL L16 4 RN
L17 1 S E1/RN
SET TERMSET LOGIN

FILE 'IMSPATENTS' ENTERED AT 20:31:27 ON 09 NOV 2006

L18 94 S L17

FILE 'REGISTRY' ENTERED AT 20:31:36 ON 09 NOV 2006

L19 1 S DIVALPROEX SODIUM
L20 17 S VALPROIC ACID

FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 20:32:48 ON 09 NOV 2006

L21 41259 S 103-90-2/RN OR ACETAMINOPHEN OR TYLENOL OR ACETAMINOFEN OR AP
L22 41014 S 103-90-2/RN OR ACETAMINOPHEN OR TYLENOL OR ACETAMINOFEN
L23 153836 S METHOTREXATE OR 59-05-2/RN
L24 15008 S 134523-00-5/RN OR ATORVASTATIN
L25 22400 S SIMVASTATIN OR 79902-63-9/RN
L26 16267 S 59-67-6/RN
L27 28378 S 59-67-6/RN OR NIACIN OR 3-CARBOXYLPYRIDINE
L28 31733 S 86386-73-4/RN OR FLUCONAZOLE
L29 286 S 76584-70-8/RN OR DIVAPROEX SODIUM
L30 41615 S 99-66-1/RN OR VALPROIC ACID

=> s 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130
L31 323535 L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR
 L30

=> s 131 and 18
L32 348 L31 AND L8

=> s 131 and 19
L33 151 L31 AND L9

=> dup rem 132
PROCESSING COMPLETED FOR L32
L34 311 DUP REM L32 (37 DUPLICATES REMOVED)

=> dup rem 133
PROCESSING COMPLETED FOR L33
L35 147 DUP REM L33 (4 DUPLICATES REMOVED)

=> s hepato? or hepatic or liver
L36 2580162 HEPATO? OR HEPATIC OR LIVER

=> s l36 and (toxic or toxicity or hepatotoxicity or damage)
L37 345852 L36 AND (TOXIC OR TOXICITY OR HEPATOTOXICITY OR DAMAGE)

=> s l36 and l37
L38 345852 L36 AND L37

=> s l34 and l38
L39 20 L34 AND L38

=> s l35 and l38
L40 7 L35 AND L38

=> focus 139 or 140
OR IS NOT VALID HERE
The term is either unrecognized or invalid.

=> focus 139
PROCESSING COMPLETED FOR L39
L41 20 FOCUS L39 1-

=> focus 140
PROCESSING COMPLETED FOR L40
L42 7 FOCUS L40 1-

=> d ibib abs hitstr 1-20 141

L41 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:524628 CAPLUS
DOCUMENT NUMBER: 131:317404
TITLE: Nicotinamide and methionine reduce
the liver toxic effect of
methotrexate
AUTHOR(S): Kroger, H.; Hauschild, A.; Ohde, M.; Bache, K.; Voigt,
W. P.; Thefeldt, W.; Kruger, D.
CORPORATE SOURCE: Deutsches Rheumaforschungszentrum Berlin, Berlin,
10115, Germany
SOURCE: General Pharmacology (1999), 33(2), 203-206
CODEN: GEPHDP; ISSN: 0306-3623
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methotrexate is widely used as a therapeutic agent in different
diseases. This therapy is connected with various side effects, including
liver toxicity. The authors have developed a mouse
model to demonstrate the toxic effects of methotrexate
: mice were given 50 mg/kg acetaminophen, which itself has no
effect on the liver. If, addnl., methotrexate is
applied, there is an increase in the death rate, as well as in
glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate
transminase (GPT) activities. If methotrexate is administered
in conjunction with either nicotinamide or methionine,
the rise in the death rate and in GOT and GPT activities associated with

methotrexate application is markedly reduced. On the basis of these results, it can be concluded that **methotrexate** therapy should be combined with either **nicotinamide** or **methionine**, resp.

IT 59-05-2, **Methotrexate**

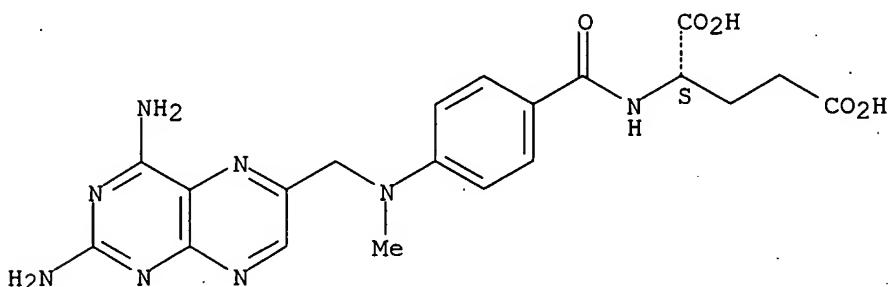
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**nicotinamide** and **methionine** reduce liver toxicity of **methotrexate**)

RN 59-05-2 CAPLUS

CN L-Glutamic acid, N-[4-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 63-68-3, L-Methionine, biological studies

98-92-0, Nicotinamide

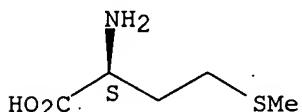
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(**nicotinamide** and **methionine** reduce liver toxicity of **methotrexate**)

RN 63-68-3 CAPLUS

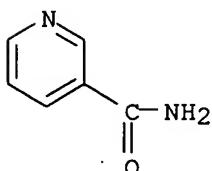
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS

CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



REFERENCE COUNT:

15

THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

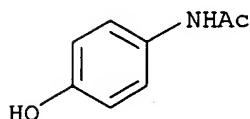
L41 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:24414 CAPLUS

DOCUMENT NUMBER: 126:126789

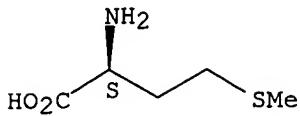
TITLE: Protection from acetaminophen-induced

liver damage by the synergistic action of low doses of the poly(ADP-ribose) polymerase-inhibitor **nicotinamide** and the antioxidant N-acetylcysteine or the amino acid L-**methionine**
 AUTHOR(S): Kroeger, H.; Dietrich, A.; Ohde, M.; Lange, R.; Ehrlich, W.; Kurpisz, M.
 CORPORATE SOURCE: DEUTSCHES RHEUMAFORSCHUNGSZENTRUM BERLIN, BERLIN,
 D-10117, Germany
 SOURCE: General Pharmacology (1997), 28(2), 257-263
 CODEN: GEPHDP; ISSN: 0306-3623
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB An array of therapeutically used analgetic and antirheumatic drugs cause severe liver damage. The present study investigates the hepatoprotective effects of inhibitors of NAD-dependent adenoribosylation reactions and of antioxidants in analgesic-induced hepatic injury. Male NMRI mice were treated PO with 500 mg/kg of acetaminophen, and the activities of both glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) were determined in serum. The acetaminophen-induced release of both GOT and GPT from injured liver cells could be inhibited in a dose-dependent manner, when mice were injected addnl. either with increasing amts. (from 25 mg/kg to 100 mg/kg IP) of the poly(ADP-ribose) polymerase (PARP)-inhibitor **nicotinamide**, with increasing amts. (from 25 mg/kg to 100 mg/kg IP) of the antioxidant N-acetylcysteine, or with increasing amts. (from 50 mg/kg to 300 mg/kg IP) of the amino acid L-**methionine**. A combination of both **nicotinamide** and N-acetylcysteine (at the low dose of 12.5 mg/kg IP each) results in a complete protection from acetaminophen-induced release of GOT and GPT from injured liver cells. A combination of both L-**methionine** and N-acetylcysteine or **nicotinamide** (at the low dose of 12.5 mg/kg IP each) resulted also in complete protection from acetaminophen-induced release of GOT and GPT.
 IT 103-90-2, Acetaminophen
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (protection from acetaminophen-induced liver damage by synergistic action of low doses of poly(ADP-ribose) polymerase-inhibitor **nicotinamide** and antioxidant N-acetylcysteine or amino acid L-**methionine**)
 RN 103-90-2 CAPLUS
 CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)

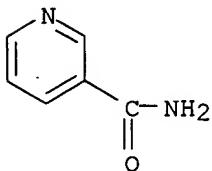


IT 63-68-3, L-Methionine, biological studies
 98-92-0, Nicotinamide
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (protection from acetaminophen-induced liver damage by synergistic action of low doses of poly(ADP-ribose) polymerase-inhibitor **nicotinamide** and antioxidant N-acetylcysteine or amino acid L-**methionine**)
 RN 63-68-3 CAPLUS
 CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1075402 CAPLUS

DOCUMENT NUMBER: 143:353368

TITLE: Compositions with reduced hepatotoxicity

INVENTOR(S): Bernstein, Joel E.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 4 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005220862	A1	20051006	US 2004-813760	20040331
WO 2005097120	A1	20051020	WO 2005-US9795	20050323
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2004-813760 A 20040331

AB Pharmaceutical compns. of hepatotoxic compds. are provided in which the hepatotoxicity of the compds. is mitigated by including quantities of nicotinamide and methionine in the composition. Folic acid also can be included to further mitigate the hepatotoxic effects. The hepatotoxic compds. can include acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium, and valproic acid.

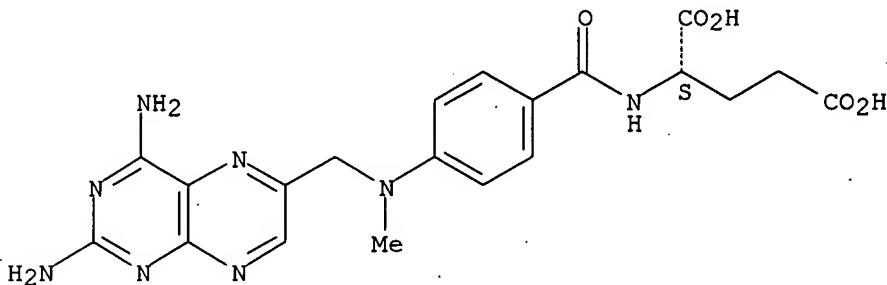
IT 59-05-2, Methotrexate 59-67-6, Niacin,
, biological studies 99-66-1, Valproic acid

103-90-2, Acetaminophen 76584-70-8, Divalproex
sodium 79902-63-9, Simvastatin 86386-73-4,
Fluconazole 134523-00-5, Atorvastatin
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(comps. with reduced hepatotoxicity)

RN 59-05-2 CAPLUS

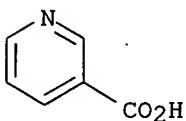
CN L-Glutamic acid, N-[4-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzo
yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



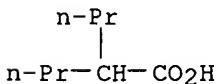
RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



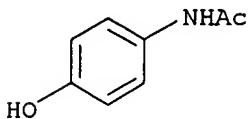
RN 99-66-1 CAPLUS

CN Pentanoic acid, 2-propyl- (9CI) (CA INDEX NAME)



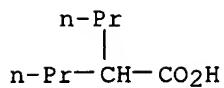
RN 103-90-2 CAPLUS

CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 76584-70-8 CAPLUS

CN Pentanoic acid, 2-propyl-, sodium salt (2:1) (9CI) (CA INDEX NAME)

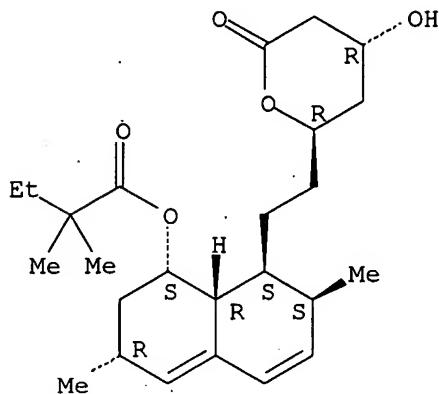


● 1/2 Na

RN 79902-63-9 CAPLUS

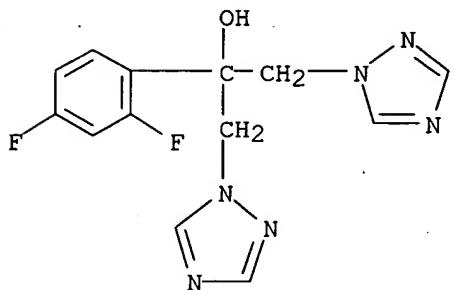
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 86386-73-4 CAPLUS

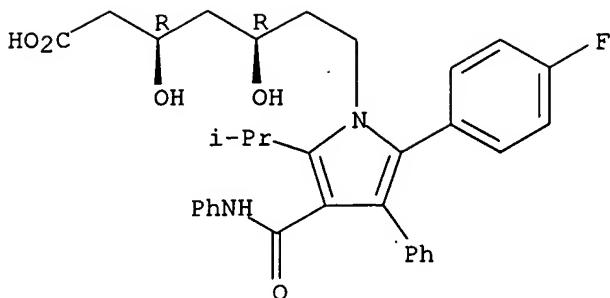
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 134523-00-5 CAPLUS

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (βR,δR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 63-68-3, Methionine, biological studies 98-92-0

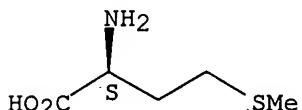
, Nicotinamide

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. with reduced hepatotoxicity)

RN 63-68-3 CAPLUS

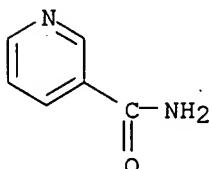
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS

CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



L41 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1980:420038 CAPLUS

DOCUMENT NUMBER: 93:20038

TITLE: Long-term perturbation of pyridine nucleotides in rat liver

AUTHOR(S): Sturm, Gerlinde; Staerk, Doris; Spengler, Ulrike;
Nittlinger, Juergen; Jaus, Heinrich H.; Graessle,
Barbel; Siebert, Guenther; Romen, Werner

CORPORATE SOURCE: Inst. Biol. Chem. Ernaehrungswiss., Univ. Hohenheim,
Fed. Rep. Ger.

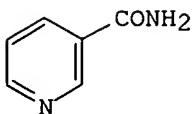
SOURCE: Hoppe-Seyler's Zeitschrift fuer Physiologische Chemie
(1980), 361(4), 551-8

CODEN: HSZPAZ; ISSN: 0018-4888

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB During a treatment of rats with 4 mmol of **nicotinamide** (I) [98-92-0]/kg daily at 12-h intervals for several weeks a permanent rise of **liver** NAD [53-84-9] by several hundred percent is effected; NADP [53-59-8] + NADPH [53-57-6] also increase slightly. Male and female animals of the SIV-50 strain differ in normal and in elevated NAD values; female rats react more markedly and present more pronounced alterations of the **liver**. Besides **nicotinamide**, large amts. of N1-methylnicotinamide [3106-60-3] and nicotinuric acid [583-08-4] and also small amts. of **nicotinamide** N-oxide [1986-81-8] are excreted into the urine. Nicotinuric acid, an unexpected metabolite, was crystallized from urine and identified unequivocally. A permanent load of rats with 1 g **nicotinamide**/kg daily leads to alterations of the **liver** which manifest themselves macroscopically, by hepatocyte enlargement, glycogen [9005-79-2] deposits, enzyme decreases, and eventually fatty degeneration. When extra L-methionine [63-68-3] and glycine [56-40-6] are given in the diet, **liver** alterations are much less severe. It is concluded that the treatment with **nicotinamide** causes a severe amino acid imbalance. During the treatment, animals show symptoms of catatonic stupor, which is discussed in connection with proposals of a **nicotinamide** megatherapy against schizophrenia. On the whole, the exptl. system of permanently elevated NAD concns. is combined with rather serious disadvantages; it is not regarded as a very good general model in studies of **liver** NAD.

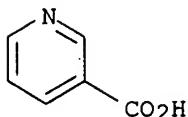
IT 59-67-6, biological studies

RL: BIOL (Biological study)

(as **nicotinamide** metabolite, **nicotinamide** effects of **liver** pyridine nucleotides in relation to)

RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



IT 63-68-3, biological studies

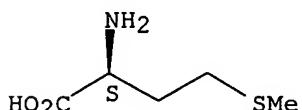
RL: BIOL (Biological study)

(**nicotinamide** induction of **liver** toxicity reversal by glycine and)

RN 63-68-3 CAPLUS

CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

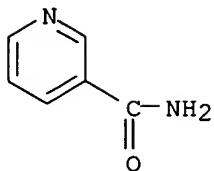


IT 98-92-0

RL: PRP (Properties)

(pyridine nucleotides of **liver** response to, **liver**

toxicity in relation to)
RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



L41 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1154777 CAPLUS
DOCUMENT NUMBER: 143:433974
TITLE: Gene expression profiling and markers for use in the assessment of hepatotoxicity
INVENTOR(S): Porter, Mark; Higgs, Brandon; Mendrick, Donna;
Elashoff, Michael
PATENT ASSIGNEE(S): Gene Logic, Inc., USA
SOURCE: PCT Int. Appl., 264 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005100989	A2	20051027	WO 2005-US11532	20050407
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2004-559949P P 20040407
AB Methods of using the effects of a substance on gene expression profiles are described for use in assessing their toxicity, especially hepatotoxicity, are described. The invention also includes microarrays, computer systems comprising the toxicity prediction models, as well as methods of using the computer systems by remote users for determining the toxicity of test agents. A database of gene expression profiles for rat liver using a broad range of drugs, com. chems., and known poisons is developed.

IT 59-05-2 99-66-1 103-90-2 79902-63-9.

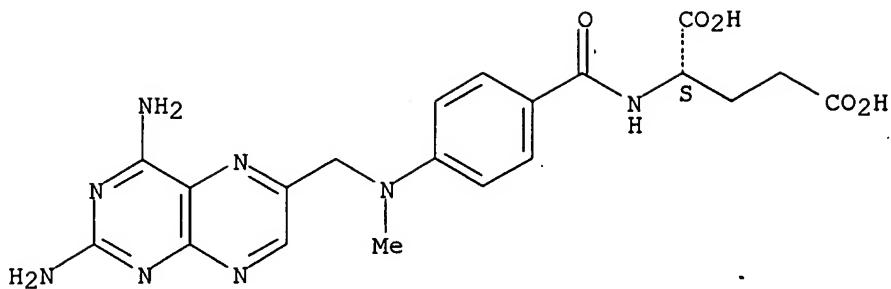
Simvastatin

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(assessing hepatotoxicity of; gene expression profiling and markers for use in assessment of hepatotoxicity)

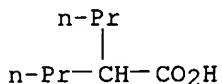
RN 59-05-2 CAPLUS

CN L-Glutamic acid, N-[4-[[[2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]- (9CI) (CA INDEX NAME)

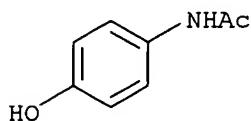
Absolute stereochemistry.



RN 99-66-1 CAPLUS
CN Pentanoic acid, 2-propyl- (9CI) (CA INDEX NAME)

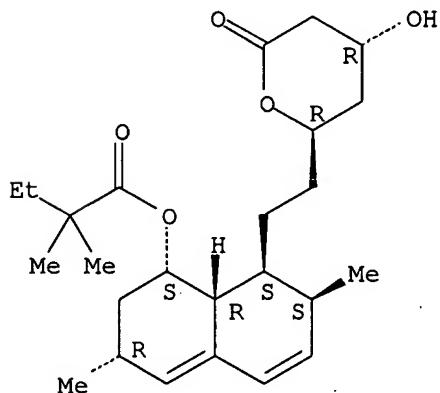


RN 103-90-2 CAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L41 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:47659 CAPLUS
DOCUMENT NUMBER: 124:169433
TITLE: Methylene blue plus light-induced lipid peroxidation
in rat liver microsomes: inhibition by
nicotinamide (vitamin B3) and other

AUTHOR(S): antioxidants
 Kamat, Jayashree P.; Devasagayam, Thomas P. A.
 CORPORATE SOURCE: Bombay-400, India
 SOURCE: Chemico-Biological Interactions (1996), 99(1-3), 1-16
 CODEN: CBINA8; ISSN: 0009-2797
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English

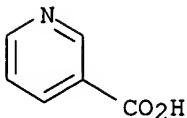
AB Methylene blue plus visible light, in the presence of oxygen, induced lipid peroxidn. in rat liver microsomes, as assessed by the formation of thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides and the loss of membrane-bound enzymes. Peroxidn. was enhanced by deuteration of the buffer and inhibited by scavengers of singlet oxygen ($1O_2$) and superoxide (O_2^-). The damage induced seemed to be mainly due to Type II involving $1O_2$ and to a lesser extent Type I reactions with O_2^- and hydroxyl radical (OH) as intermediates. Nicotinamide or vitamin B3, an endogenous metabolite occurring at high concns. in tissues, had a relatively high rate constant of $1.8 + 108$ M $^{-1}$ s $^{-1}$ with $1O_2$ and had a significant inhibitory effect on lipid peroxidn. induced by photosensitization. This effect was both time- and concentration-dependent, high inhibition being associated with millimolar concns.

Chemical related endogenous compds. like tryptophan and isonicotinic acid also had significant inhibitory properties. Similar protective effects were observed with natural antioxidants such as β -carotene, canthaxanthin, lipoic acid, glutathione, α -tocopherol and to a lesser extent ascorbic acid. Nicotinamide was a more effective antioxidant than ascorbic acid. It also showed a similar inhibitory effect against NADPH-ADP-Fe $^{3+}$ -induced lipid peroxidn. Our results suggest that nicotinamide had significant ability to protect against photosensitization-induced cytotoxicity and cell damage and that it may do so by its ability to react with $1O_2$ and other reactive oxygen species.

IT 59-67-6, 3-Pyridinecarboxylic acid, biological studies
 63-68-3, Methionine, biological studies 98-92-0
 , Nicotinamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (methylene blue plus light-induced lipid peroxidn. in rat liver microsomes: nicotinamide (vitamin B3) and other antioxidants)

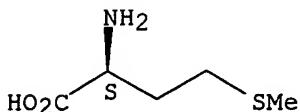
RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



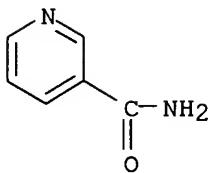
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS

CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



L41 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1959:101245 CAPLUS

DOCUMENT NUMBER: 53:101245

ORIGINAL REFERENCE NO.: 53:18278h-i,18279a

TITLE:

The need of combining **methionine** with
nicotinic acid and **nicotinamide** when
administering these pyridine compounds in very high
doses

AUTHOR(S): Cedrangolo, F.; Scala, E.

CORPORATE SOURCE: Univ. Naples

SOURCE: Minerva Medica (1959) 1299

CODEN: MIMEAO; ISSN: 0026-4806

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

AB Since both nicotinic acid and **nicotinamide** (I) are eliminated as N-methyl-2-pyridonecarboxamide, high doses lead to rapid depletion of Me group reserve, with serious results such as fatty degeneration of the liver. In rats, 0.5 g. of I/100 g. of diet causes considerable fatty degeneration in the liver, together with renal hemorrhage (Foa, et al., C.A. 39, 4654). In normal humans, 400 mg./day has shown signs of **hepatic** insufficiency as a pos. Wallace-Diamond test (Scala and Janella, C.A. 51, 9940i). This has now been confirmed in numerous patients. Doses of I over 100 mg. should be combined with suitable amts. of **methionine**.

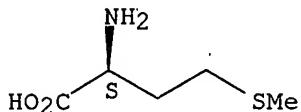
IT 63-68-3, Methionine

(in **nicotinamide** and **nicotinic acid** treatment)

RN 63-68-3 CAPLUS

CN L-Methionine (9CI) (CA INDEX NAME)

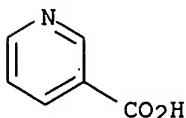
Absolute stereochemistry.



IT 59-67-6, Nicotinic acid 98-92-0, Nicotinamide
(toxicity of, **methionine** prevention of)

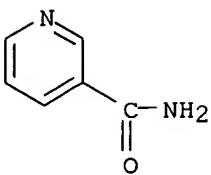
RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)

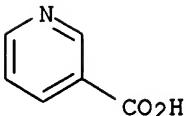


RN 98-92-0 CAPLUS

CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)

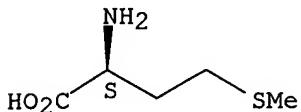


L41 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:443026 CAPLUS
 DOCUMENT NUMBER: 144:102210
 TITLE: Profiles of Metabolites and Gene Expression in Rats with Chemically Induced **Hepatic** Necrosis
 AUTHOR(S): Heijne, Wilbert; Lamers, Robert-Jan; Van Bladeren, Peter; Grotens, John; Van Nesselrooij, Joop; Van Ommen, Ben
 CORPORATE SOURCE: TNO Nutrition and Food Research, Zeist, Neth.
 SOURCE: Toxicologic Pathology (2005), 33(4), 425-433
 CODEN: TOPADD; ISSN: 0192-6233
 PUBLISHER: Taylor & Francis, Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB This study investigated whether integrated anal. of transcriptomics and metabolomics data increased the sensitivity of detection and provided new insight in the mechanisms of **hepatotoxicity**. Metabolite levels in plasma or urine were analyzed in relation to changes in **hepatic** gene expression in rats that received bromobenzene to induce acute **hepatic** centrilobular necrosis. Bromobenzene-induced lesions were only observed after treatment with the highest of 3 dose levels. Multivariate statistical anal. showed that metabolite profiles of blood plasma were largely different from controls when the rats were treated with bromobenzene, also at doses that did not elicit histopathol. changes. Changes in levels of genes and metabolites were related to the degree of necrosis, providing putative novel markers of **hepatotoxicity**. Levels of endogenous metabolites like alanine, lactate, tyrosine and dimethylglycine differed in plasma from treated and control rats. The metabolite profiles of urine were found to be reflective of the exposure levels. This integrated anal. of **hepatic** transcriptomics and plasma metabolomics was able to more sensitively detect changes related to **hepatotoxicity** and discover novel markers. The relation between gene expression and metabolite levels was explored and addnl. insight in the role of various biol. pathways in bromobenzene-induced **hepatic** necrosis was obtained, including the involvement of apoptosis and changes in glycolysis and amino acid metabolism
 IT 59-67-6, 3-Pyridinecarboxylic acid, biological studies
 63-68-3, L-Methionine, biological studies
 98-92-0, Nicotinamide
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (profiles of metabolites and gene expression in rats with chemical induced **hepatic** necrosis)
 RN 59-67-6 CAPLUS
 CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)

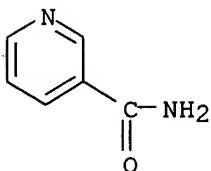


RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



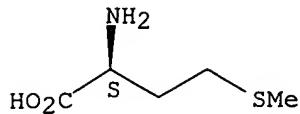
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1958:41446 CAPLUS
DOCUMENT NUMBER: 52:41446
ORIGINAL REFERENCE NO.: 52:7475c-f
TITLE: Role of **methionine** in the metabolism of tryptophan by rats treated with carbon tetrachloride
AUTHOR(S): Banerjee, Sachchidananda; Chattopadhyay, Dhurjatiprasad
CORPORATE SOURCE: Presidency Coll., Calcutta
SOURCE: Indian Journal of Medical Research (1913-1988) (1957), 45, 531-5
CODEN: IJMRAQ; ISSN: 0019-5340
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

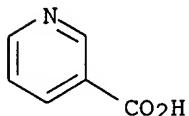
AB The injection of CC₁₄ caused a decrease in urinary excretions of nicotinic acid (I), quinolinic acid (II), N1-methyl **nicotinamide** (III) and creatinine (IV). It possibly indicated that the **liver** had been damaged and could not synthesize I efficiently from tryptophan. When the rats were injected with **methionine**, although there was no change in the urinary secretion of I and II, a significant increase in the urinary excretion of III and IV was noted indicating that the labile CH₃ group of **methionine** helps the methylating mechanism. When CC₁₄ was injected along with the injection of **methionine**, no decrease in the urinary excretions of, I, II, III, or IV was observed. It therefore seems that **methionine** somehow protects the animal from CC₁₄ poisoning. Total fat, free cholesterol and esterified cholesterol contents of livers of CC₁₄ injected rats were higher than the corresponding values in normal rats. Simultaneous injection of **methionine** prevented the accumulation of increased amts. of lipides in the **liver**. CC₁₄ poisoning did not affect the intestine indicating that the **liver** is the principal site of synthesis of I from tryptophan in rats.

IT 63-68-3, Methionine
(effect on tryptophan metabolism in **liver damage**)
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 59-67-6, Nicotinic acid
(in urine, in liver disorder, methionine effect on)
RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



L41 ANSWER 10 OF 20 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005348235 EMBASE

TITLE: Protection from acetaminophen-induced liver damage by the synergistic action of low doses of the poly(ADP-ribose) polymerase-inhibitor nicotinamide and the antioxidant N-acetylcysteine or the amino acid L-methionine.

AUTHOR: Kroger H.; Dietrich A.; Ohde M.; Lange R.; Ehrlich W.; Kurpisz M.

CORPORATE SOURCE: H. Kroger, Deutsches Rheumafororschungszentrum Berlin, Monbijoustr. 2, D-10117 Berlin, Germany

SOURCE: Vascular Pharmacology, (1997) Vol. 28, No. 2, pp. 257-263.

Refs: 32

ISSN: 1537-1891 CODEN: VPAHAJ

PUBLISHER IDENT.: S 0306-3623(96)00181-4

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 1 Sep 2005
Last Updated on STN: 1 Sep 2005

AB An array of therapeutically used analgetic and antirheumatic drugs cause severe liver damage. The present study investigates the hepatoprotective effects of inhibitors of NAD-dependent adenoribosylation reactions and of antioxidants in analgesic-induced hepatic injury. Male NMRI mice were treated PO with 500 mg/kg of acetaminophen, and the activities of both glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) were determined in serum. The acetaminophen-induced release of both GOT and GPT from injured liver cells could be inhibited in a dose-dependent manner, when mice were injected additionally either with increasing amounts (from 25 mg/kg to 100 mg/kg IP) of the PARP-inhibitor nicotinamide, with increasing amounts (from 25 mg/kg to 100 mg/kg IP) of the antioxidant N-acetylcysteine, or with increasing amounts (from 50 mg/kg to 300 mg/kg IP) of the amino acid L-methionine. A combination of both nicotinamide and N-acetylcysteine (at the low dose of 12.5 mg/kg IP each) results in a complete protection from

acetaminophen-induced release of GOT and GPT from injured liver cells. A combination of both L-**methionine** and N-acetylcysteine or **nicotinamide** (at the low dose of 12.5 mg/kg IP each) resulted also in complete protection from **acetaminophen**-induced release of GOT and GPT. Copyright .COPYRGT. 1997 Elsevier Science Inc.

L41 ANSWER 11 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002462179 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12221238
TITLE: Acute valproate administration impairs **methionine** metabolism in rats.
AUTHOR: Ubeda Natalia; Alonso-Aperte Elena; Varela-Moreiras Gregorio
CORPORATE SOURCE: Seccion de Nutricion, Bromatologia y Dietetica, Facultad de Ciencias Experimentales y de la Salud, Universidad San Pablo CEU, Madrid, Spain.. nubeda@ceu.es
SOURCE: The Journal of nutrition, (2002 Sep) Vol. 132, No. 9, pp. 2737-42.
Journal code: 0404243. ISSN: 0022-3166.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 11 Sep 2002
Last Updated on STN: 7 Feb 2003
Entered Medline: 6 Feb 2003

AB Valproate (VPA) is a drug widely used to treat epilepsy, but it has serious adverse effects including **hepatotoxicity**, teratogenicity and antifolate activity. The mechanism underlying VPA **toxicity** is unclear although an interaction with folate and other metabolites involved in **methionine** metabolism has been suggested. The present study was undertaken to evaluate potential changes in the metabolic function of the **methionine** cycle after acute exposure to a single dose of valproate. Female Wistar rats (n = 30) were treated with 400 mg/kg of VPA. Different groups of six rats were killed at 1 (t1), 3 (t3), 6 (t6), 9 (t9), and 24 (t24) hours after the injection. One group of rats was untreated (n = 6) and was considered the control group. The most pronounced effects of VPA administration were observed 1 h after drug injection. VPA induced a 56% reduction in **methionine** adenosyltransferase activity and a 54% reduction in plasma **vitamin B-6**. Increases in the **hepatic** concentration of S-adenosylhomocysteine and oxidized glutathione, and a reduction in the S-adenosylmethionine/S-adenosylhomocysteine transmethylation ratio also occurred at 1 h. All of these alterations, however, were normalized within 24 h, parallel with a decrease in serum VPA concentration. The acute effects of VPA suggest that the alterations in the **methionine** cycle could be the common mechanism underlying the **hepatotoxic**, teratogenic and antifolate effects of the drug.

L41 ANSWER 12 OF 20 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 97048562 EMBASE
DOCUMENT NUMBER: 1997048562
TITLE: Male rats fed methyl- and folate-deficient diets with or without **niacin** develop **hepatic** carcinomas associated with decreased tissue NAD concentrations and altered poly(ADP-ribose) polymerase activity.
AUTHOR: Henning S.M.; Swendseid M.E.; Coulson W.F.
CORPORATE SOURCE: S.M. Henning, Community Health Sciences, School of Public Health, University of California, Los Angeles, CA 90095,

SOURCE: United States
Journal of Nutrition, (1997) Vol. 127, No. 1, pp. 30-36.
Refs: 26
ISSN: 0022-3166 CODEN: JONUAI

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 1997
Last Updated on STN: 10 Mar 1997

AB Folate is an essential cofactor in the generation of endogenous methionine, and there is evidence that folate deficiency exacerbates the effects of a diet low in choline and methionine, including alterations in poly(ADP-ribose) polymerase (PARP) activity, an enzyme associated with DNA replication and repair. Because PARP requires NAD as its substrate, we postulated that a deficiency of both folate and niacin would enhance the development of liver cancer in rats fed a diet deficient in methionine and choline. In two experiments, rats were fed choline- and folate-deficient, low methionine diets containing either 12 or 8% casein (12% MCFD, 8% MCFD) or 6% casein and 6% gelatin with niacin (MCFD) or without niacin (MCFND) and were compared with folate-supplemented controls. Liver NAD concentrations were lower in all methyl-deficient rats after 2-17 mo. At 17 mo, NAD concentrations in other tissues of rats fed these diets were also lower than in controls. Compared with control values, liver PARP activity was enhanced in rats fed the 12% MCFD diet but was lower in MCFND-fed rats following a further reduction in liver NAD concentration. These changes in PARP activity associated with lower NAD concentrations may slow DNA repair and enhance DNA damage. Only rats fed the MCFD and MCFND diets developed hepatocarcinomas after 12-17 mo. In Experiment 2, hepatocarcinomas were found in 100% of rats fed the MCFD and MCFND diets. These preliminary results indicate that folic acid deficiency enhances tumor development. Because tumors developed in 100% of the MCFD-fed rats and because tissue concentrations of NAD in these animals were also low, further studies are needed to clearly define the role of niacin in methyldeficient rats.

L41 ANSWER 13 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002162732 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11895163
TITLE: Niacin (nicotinic acid) in non-physiological doses causes hyperhomocysteinaemia in Sprague-Dawley rats.
AUTHOR: Basu Tapan K; Makhani Neelam; Sedgwick Gary
CORPORATE SOURCE: Department of Agricultural, Food and Nutritional Science,
University of Alberta, Edmonton, Canada..
tbasu@afns.ualberta.ca
SOURCE: The British journal of nutrition, (2002 Feb) Vol. 87, No. 2, pp. 115-9.
Journal code: 0372547. ISSN: 0007-1145.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 17 Mar 2002
Last Updated on STN: 23 Apr 2002
Entered Medline: 22 Apr 2002

AB Niacin (nicotinic acid) in its non-physiological dose level is known to be an effective lipid-lowering agent; its potential risk as a

therapeutic agent, however, has not been critically considered. Since niacin is excreted predominantly as methylated pyridones, requiring methionine as a methyl donor, the present study was undertaken to examine whether metabolism of the amino acid is altered in the presence of large doses of niacin. Male Sprague-Dawley rats were given a nutritionally adequate, semi-synthetic diet containing niacin at a level of either 400 or 1000mg/kg diet (compared to 30mg/kg in the control diet) for up to 3 months. Supplementation with niacin (1,000 mg/kg diet) for 3 months resulted in a significant increase in plasma and urinary total homocysteine levels; this increase was further accentuated in the presence of a high methionine diet. The hyperhomocysteinaemia was accompanied by a significant decrease in plasma concentrations of vitamins B6 and B12, which are cofactors for the metabolism of homocysteine. The homocysteine-raising action of niacin, in particular, has an important toxicological implication, as hyperhomocysteinaemia is considered to be an independent risk factor for arterial occlusive disease. The niacin-associated change in homocysteine status may be an important limiting factor in the use of this vitamin as a lipid-lowering agent.

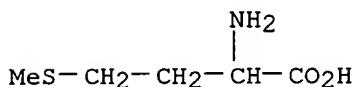
L41 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN.
 ACCESSION NUMBER: 2004:162309 CAPLUS
 DOCUMENT NUMBER: 140:205217
 TITLE: System for exsanguinous metabolic support of an organ or tissue
 INVENTOR(S): Brasile, Lauren
 PATENT ASSIGNEE(S): Breonics, Inc., USA
 SOURCE: U.S. Pat. Appl. Publ., 25 pp., Cont.-in-part of U.S. Ser. No. 849,618.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004038192	A1	20040226	US 2003-443452	20030522
US 6642045	B1	20031104	US 2000-547843	20000412
US 2002012988	A1	20020131	US 2001-849618	20010504
US 6582953	B2	20030624		
US 2004038193	A1	20040226	US 2003-650986	20030827
WO 2004105484	A1	20041209	WO 2004-US16085	20040521
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 1999-129257P	P 19990414
			US 2000-547843	A2 20000412
			US 2001-849618	A2 20010504
			WO 2000-US9894	W 20000413
			US 2003-443452	A 20030522

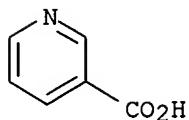
AB An exsanguinous metabolic support system for maintaining an organ or tissue at a near normal metabolic rate is disclosed that employs a warm perfusion solution capable of altering the production of nitric oxide (NO) in an

organ or tissue and supporting the metabolism of the organ or tissue at normothermic temps. Perfusion with the solution of the invention can therefore be used to regulate nitric oxide production in situations where it is desirable to do so, e.g. to prevent reperfusion injury. The system also monitors parameters of the circulating perfusion solution, such as pH, temperature, osmolarity, flow rate, vascular pressure and partial pressure of respiratory gases, and nitric oxide (NO) concentration and regulates them to insure that the organ is maintained under near-physiol. conditions. Use of the system for long-term maintenance of organs for transplantation, for resuscitation and repair of organs having sustained warm ischemic damage, to treat cardiovascular disorders, to prevent reperfusion injury, as a pharmaceutical delivery system and prognosticator of post-transplantation organ function is also disclosed.

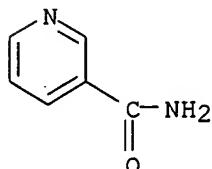
IT 59-51-8, **Methionine** 59-67-6, Nicotinic Acid,
biological studies 98-92-0, **Niacinamide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(system for exsanguinous metabolic support of an organ or tissue)
RN 59-51-8 CAPLUS
CN Methionine (9CI) (CA INDEX NAME)



RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



L41 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1953:32699 CAPLUS
DOCUMENT NUMBER: 47:32699
ORIGINAL REFERENCE NO.: 47:5557i,5558a-d
TITLE: Pharmacological studies on isonicotinic acid hydrazide
AUTHOR(S): Garattini, S.; Grassi, C.; Mantegazza, P.; Morvillo, V.; Tommasini, R.; Trabucchi, E.
CORPORATE SOURCE: Univ. Milan
SOURCE: Atti della Societa Lombarda di Scienze Mediche e Biologiche (1952), 7(No. Spec.), 1-19; English summary 18-19
CODEN: ASLBAG; ISSN: 0365-690X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

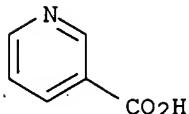
AB Isonicotinic acid hydrazide (I) showed a more intense inhibiting action than streptomycin on Koch's bacilli in vitro. Vitamins B1, B2, and B6, p-aminobenzoic acid, uracil, thymine, **nicotinamide**, choline, **methionine**, folic acid, pantothenic acid, isonicotinic acid, and isonicotinamide were inefficient in counteracting I action. (1) p-Aminobenzoic acid hydrazide, nicotinic acid hydrazide, and isonicotinic acid amide, (2) succinic acid bishydrazide, and (3) pyrazincarboxylic acid hydrazide had, resp., (1) no, (2) some, and (3) a considerable inhibiting action on Koch's bacilli. Also in vivo, in rats, the effect of I was higher than that of streptomycin. Intravenously injected I was distributed rapidly to the various tissues, especially to **liver**; exchanges through the blood-tissue barrier occurred in both senses; I urinary excretion occurred within some hrs. after injection. I was rapidly destroyed in the organism (removal of both the terminal N, with formation of NH₃ and isonicotinamide, and of the whole hydrazine group with formation of isonicotinic acid). Also in vitro I was decomposed (lateral chain taken off) by slices of **liver**, lung, and brain and by yeasts; this action was inhibited by thiourea and p-aminobenzoic acid. Metabolisms of I and of isonicotinic acid and its amide were different from that of **nicotinamide** since the pyridine N was not alkylated. The nervous phenomena due to I administration to animals were also investigated: the association of thiourea and p-aminobenzoic acid with I attenuated its convulsive effect, the association of pyruvic acid enhanced the resistance of animals to the **toxic** effects of I. The administration of I lowered the pyruvic acid level of blood in humans and animals (and of the brain of the latter), and in sound subjects caused also a drop of blood eosinophils and in guinea pigs a considerable drop of the ascorbic acid content of adrenal glands (by high I doses).

IT 59-67-6, Nicotinic acid

(hydrazides, bacteriostatic action on tubercle bacilli)

RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



L41 ANSWER 16 OF 20 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001398967 EMBASE

TITLE: Folic acid revisited.

AUTHOR: Hazra A.; Kumar Tripathi S.

CORPORATE SOURCE: A. Hazra, 17/2/4B Chakraberia Road (South), Calcutta 700025, India. blowfans@cal2.vsnl.net.in

SOURCE: Indian Journal of Pharmacology, (2001) Vol. 33, No. 5, pp. 322-342.

Refs: 114

ISSN: 0253-7613 CODEN: INJPDD

COUNTRY: India

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 029 Clinical Biochemistry

030 Pharmacology

017 Public Health, Social Medicine and Epidemiology

037 Drug Literature Index

025 Hematology

020 Gerontology and Geriatrics

021 Developmental Biology and Teratology

036 Health Policy, Economics and Management

005 General Pathology and Pathological Anatomy

038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 30 Nov 2001

Last Updated on STN: 30 Nov 2001

AB Folic acid, or pteroylglutamic acid, is a well-known water soluble vitamin of the B-complex group. It is necessary for DNA synthesis and normal erythropoiesis. Tetrahydrofolate, the active form of this vitamin, functions as a coenzyme in various metabolic reactions involving transfer of one-carbon moieties. Folate and **vitamin B(12)** metabolic pathways intersect at the conversion of homocysteine to **methionine**. Human beings cannot synthesize this vitamin and must obtain performed folate through dietary sources like green leafy vegetables, cereals, fruits, organ meats and yeast. Synthetic folic acid is more bioavailable than food folate. Absorption is predominantly from the upper small intestine and elimination predominantly renal, with modest **hepatic** storage. The daily requirement varies by age and is greater during pregnancy and lactation. Apart from increased demand, folate deficiency can occur in malnutrition, malabsorption, chronic hemolytic anemias, chronic alcoholism, repeated hemodialysis, and unusual dietary situations like total parenteral nutrition. The use of certain antiepileptic, antimalarial, antimicrobial and anticancer drugs may interfere with the absorption, conversion or utilization of folate leading to megaloblastic anemia. The primary therapeutic indication is in the prophylaxis and treatment of deficiency states. Pharmacological supplementation is recommended in situations like pregnancy (for preventing macrocytic anemia, occurrence or recurrence of neural tube defects, counteracting teratogenic effect of anticonvulsants, etc.), malnutrition, malabsorption and chronic hemodialysis. It may be supplemented during lactation, in infants, the elderly, alcoholics, and in renal failure patients. Folic acid may also reduce orofacial clefting and ameliorate **methotrexate toxicity** in rheumatoid arthritis. Pharmacological dose are well-tolerated but folate supplementation alone in megaloblastic anemia primarily due to **vitamin B(12)** deficiency can worsen the neurological condition. Of late, interest in folic acid has grown with the realization that modest folate supplementation can prevent hyperhomocysteinemia, which is an independent graded risk factor for atherosclerotic cardiovascular disease, and is possibly beneficial in certain cancers. The recent stipulation for mandatory folate fortification of cereal products in USA and the inclusion of folic acid in the WHO model list of essential drugs recognize the increasing importance of folate in human nutrition. Indeed, folic acid has revisited with new therapeutic applications and its mysteries are still unfolding more than 7 decades after its discovery.

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ACCESSION NUMBER: 2002185488 EMBASE

TITLE: S-adenosyl-L-methionine (SAMe) for the treatment of acetaminophen toxicity in a dog.

AUTHOR: Wallace K.P.; Center S.A.; Hickford F.H.; Warner K.L.; Smith S.

CORPORATE SOURCE: K.P. Wallace, Department of Clinical Sciences, New York State Coll. Veterinary Med., Cornell University, P.O. Box 25, Ithaca, NY 14853-6401, United States

SOURCE: Journal of the American Animal Hospital Association, (2002) Vol. 38, No. 3, pp. 246-254..

Refs: 53

ISSN: 0587-2871 CODEN: JAAHBL

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 025 Hematology
030 Pharmacology

037 Drug Literature Index
052 Toxicology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 6 Jun 2002

Last Updated on STN: 6 Jun 2002

AB An 8-month-old, spayed female Shetland sheepdog presented 48 hours after ingesting **acetaminophen** (1 gm/kg body weight). On presentation, the dog was laterally recumbent and hypovolemic. The dog had brown mucous membranes, severe Heinz-body hemolytic anemia, bleeding tendencies, and a red blood cell (RBC) glutathione (GSH) concentration that was 10% of reference values, despite a regenerative erythroid response. Treatment with **s-adenosyl-L-methionine** (SAMe) as a GSH donor successfully rescued this dog, despite the animal's late presentation after drug ingestion. A loading dose (40 mg/kg body weight) of a stable SAMe salt per os was followed by a maintenance dose (20 mg/kg body weight) sid for 7 days. Additional therapeutic interventions included an intravenous (IV) infusion of one unit of packed RBCs (on admission), IV fluid support (3 days), and famotidine (7 days) to reduce gastric acidity. Sequential assessment of RBC GSH concentrations and RBC morphology documented response to antidote administration within 72 hours. This case suggests that SAMe may provide a therapeutic option for treatment of **acetaminophen** toxicosis in dogs capable of retaining an orally administered antidote and maintaining adequate **hepatic** function for metabolism of SAMe to its thiol substrates.

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ACCESSION NUMBER: 2005118231 EMBASE

TITLE: Inhibition of CYP2E1 catalytic activity in vitro by S-adenosyl-L-methionine.

AUTHOR: Caro A.A.; Cederbaum A.I.

CORPORATE SOURCE: A.A. Caro, Dept. of Pharmacol. and Biol. Chem., Mount Sinai School of Medicine, New York, NY 10029, United States.

andres.caro@mssm.edu

SOURCE: Biochemical Pharmacology, (1 Apr 2005) Vol. 69, No. 7, pp. 1081-1093.

Refs: 44

ISSN: 0006-2952 CODEN: BCPCA6

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology

037 Drug Literature Index

048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 7 Apr 2005

Last Updated on STN: 7 Apr 2005

AB The objective of this work was to evaluate the possible in vitro interactions of **S-adenosyl-L-methionine** (SAM) and its metabolites **S-(5'-Adenosyl)-l-homocysteine** (SAH), **5'-Deoxy-5'-(methylthio)** adenosine (MTA) and **methionine** with cytochrome P450 enzymes, in particular CYP2E1. SAM (but not SAH, MTA or **methionine**) produced a type II binding spectrum with **liver** microsomal cytochrome P450 from rats treated with acetone or isoniazid to induce CYP2E1. Binding was less effective for control microsomes. SAM did not alter the carbon monoxide binding spectrum of P450, nor denature P450 to P420, nor inhibit the activity of NADPH-P450 reductase. However, SAM inhibited the catalytic activity of CYP2E1 with typical substrates such as **p-nitrophenol**, ethanol, and dimethylnitrosamine, with an IC(50) around 1.5-5 mM. SAM was a non-competitive inhibitor of CYP2E1 catalytic activity and its inhibitory actions could not be mimicked by **methionine**, SAH or MTA. However, SAM did not inhibit the

oxidation of ethanol to α -hydroxyethyl radical, an assay for hydroxyl radical generation. In microsomes engineered to express individual human P450s, SAM produced a type II binding spectrum with CYP2E1-, but not with CYP3A4-expressing microsomes, and SAM was a weaker inhibitor against the metabolism of a specific CYP3A4 substrate than a specific CYP2E1 substrate. SAM also inhibited CYP2E1 catalytic activity in intact HepG2 cells engineered to express CYP2E1. These results suggest that SAM interacts with cytochrome P450s, especially CYP2E1, and inhibits the catalytic activity of CYP2E1 in a reversible and non competitive manner. However, SAM is a weak inhibitor of CYP2E1. Since the K(i) for SAM inhibition of CYP2E1 activity is relatively high, inhibition of CYP2E1 activity is not likely to play a major role in the ability of SAM to protect against the hepatotoxicity produced by toxins requiring metabolic activation by CYP2E1 such as acetaminophen, ethanol, carbon tetrachloride, thioacetamide and carcinogens. .COPYRGT. 2005 Elsevier Inc. All rights reserved.

L41 ANSWER 19 OF 20 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004257294 EMBASE
TITLE: The effect of fibrates and other lipid-lowering drugs on plasma homocysteine levels.
AUTHOR: Dierkes J.; Westphal S.; Luley C.
CORPORATE SOURCE: Dr. J. Dierkes, Inst. of Clinica Chem./Biochemistry, University Hospital Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany. jutta.dierkes@medizin.uni-magdeburg.de
SOURCE: Expert Opinion on Drug Safety, (2004) Vol. 3, No. 2, pp. 101-111.
Refs: 84
ISSN: 1474-0338 CODEN: EODSA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 1 Jul 2004

Last Updated on STN: 1 Jul 2004

AB Hyperlipidaemia is a major risk factor for cardiovascular disease. The drugs of choice for the treatment of hyperlipidaemia are either fibrates, in the case of hypertriglyceridaemia, or statins, in the case of hypercholesterolaemia. Recently, it has been shown that some of the most prescribed fibrates cause hyperhomocysteinaemia, which itself has been recognised as a cardiovascular risk factor. In particular, fenofibrate and bezafibrate lead to a 20 - 40% elevation of plasma levels of the atherogenic amino acid homocysteine, thereby possibly counteracting the desired cardiovascular protection. The most likely mechanism for this increase is an alteration of creatine-creatinine metabolism and changes in methyl transfer. Gemfibrozil does not increase homocysteine. Statins have no effect on the plasma homocysteine concentration. The increase of plasma homocysteine after fenofibrate can be lowered by the concurrent administration of folic acid and vitamins B(12) and B(6). Thus, patients with hypertriglyceridaemia can either be concurrently treated with fenofibrate and vitamins or with gemfibrozil. 2004 .COPYRGT. Ashley Publications Ltd.

L41 ANSWER 20 OF 20 MEDLINE on STN

ACCESSION NUMBER: 90252753 MEDLINE

DOCUMENT NUMBER: PubMed ID: 2187335

TITLE: Anti-leukemic potential of methyl-cobalamin inactivation by

AUTHOR: nitrous oxide.
Abels J; Kroes A C; Ermens A A; van Kapel J; Schoester M;
Spijkers L J; Lindemans J

CORPORATE SOURCE: Institute of Hematology, Erasmus University, Rotterdam, The Netherlands.

SOURCE: American journal of hematology, (1990 Jun) Vol. 34, No. 2,
pp. 128-31. Ref: 45
Journal code: 7610369. ISSN: 0361-8609.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199006

ENTRY DATE: Entered STN: 20 Jul 1990
Last Updated on STN: 20 Jul 1990
Entered Medline: 18 Jun 1990

AB Myelo-cytotoxicity of extended nitrous oxide (N₂O) inhalation was described almost forty years ago and then incidentally applied already with temporary success for suppressing leukemia. In 1948 the accompanying megaloblastic maturation arrest was explained by inactivation of the methylcobalamin coenzyme and subsequent folate deficiency. We studied the anti-leukemic effect of N₂O on a transplantable acute leukemia in B(rown) N(orway) rats. Progression of this B,N,M(yelocytic)L(eukemia) was measured as spleen and liver weights, and leukemic blood cell counts. The deoxyuridine (dU)-suppression test provided in vitro indication of the functional folate activity of leukemic cells. Breathing of N₂O-oxygen considerably reduced but did not eradicate, BNML-proliferation. Addition of anti-metabolites, interfering with some enzyme in the folate metabolism beyond the methylcobalamin co-enzyme dependent methionine synthase step, acted at least synergistically. The anti-leukemic effect of cycloleucine, which reduces S-adenosyl-methionine synthesis by inactivation of methionine adenosyltransferase, was moderate but became much stronger with N₂O inhalation. **Methotrexate**, a potent anti-leukemic agent by inhibiting tetrahydrofolate (THF) generation through inactivation of di-HF reductase, became highly anti-BNML, even in low dosage when combined with or preceded by N₂O. 5-Fluorouracil, which inhibits methylene-THF dependent thymidilate synthase, itself was surprisingly anti-BNML, but also became much more potent with previous or concomitant N₂O exposure. Preliminary dU-suppression test results with human acute leukemia cells, exposed to N₂O and/or folate antagonists in vitro, correlated well with the in vivo BNML-experiments. Combining the anticobalamin activity of N₂O with an anti-folate therefore seems to be a promising chemotherapeutic approach.

=>

L42 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1075402 CAPLUS

DOCUMENT NUMBER: 143:353368

TITLE: Compositions with reduced hepatotoxicity

INVENTOR(S): Bernstein, Joel E.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 4 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005220862	A1	20051006	US 2004-813760	20040331
WO 2005097120	A1	20051020	WO 2005-US9795	20050323
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2004-813760 A 20040331

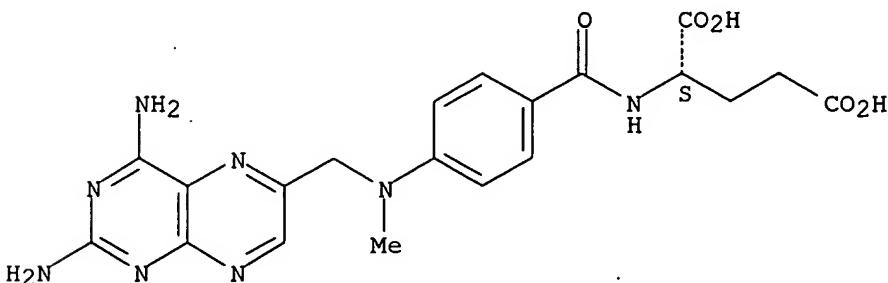
AB Pharmaceutical compns. of hepatotoxic compds. are provided in which the hepatotoxicity of the compds. is mitigated by including quantities of nicotinamide and methionine in the composition Folic acid also can be included to further mitigate the hepatotoxic effects. The hepatotoxic compds. can include acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium, and valproic acid.

IT 59-05-2, Methotrexate 59-67-6, Niacin , biological studies 99-66-1, Valproic acid 103-90-2, Acetaminophen 76584-70-8, Divalproex sodium 79902-63-9, Simvastatin 86386-73-4, Fluconazole 134523-00-5, Atorvastatin
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. with reduced hepatotoxicity)

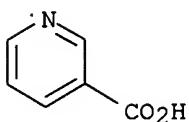
RN 59-05-2 CAPLUS

CN L-Glutamic acid, N-[4-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzo yl]- (9CI) (CA INDEX NAME)

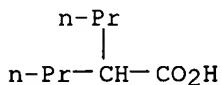
Absolute stereochemistry.



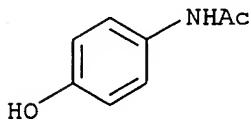
RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



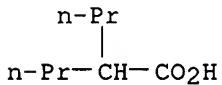
RN 99-66-1 CAPLUS
CN Pentanoic acid, 2-propyl- (9CI) (CA INDEX NAME)



RN 103-90-2 CAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



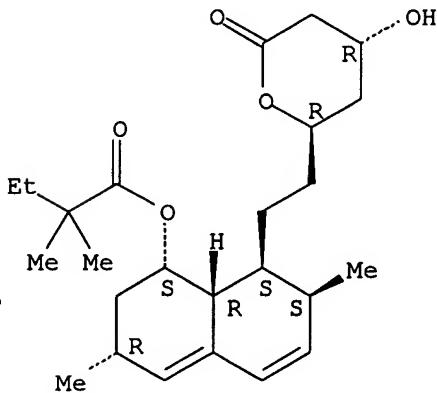
RN 76584-70-8 CAPLUS
CN Pentanoic acid, 2-propyl-, sodium salt (2:1) (9CI) (CA INDEX NAME)



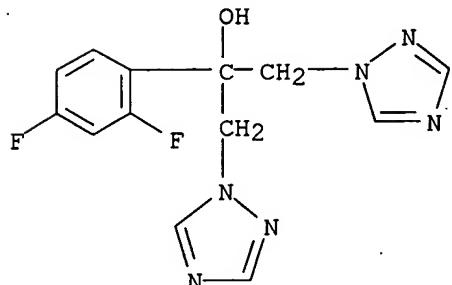
● 1/2 Na

RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

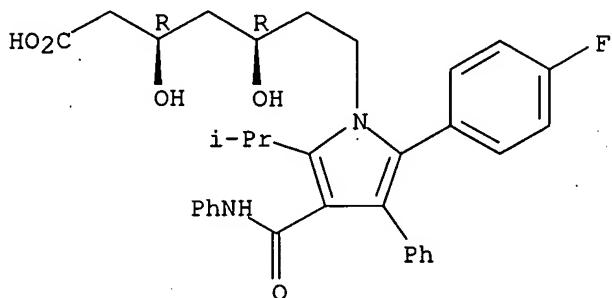


RN 86386-73-4 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α -(2,4-difluorophenyl)- α -(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 134523-00-5 CAPLUS
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (β R, δ R)- (9CI) (CA INDEX NAME)

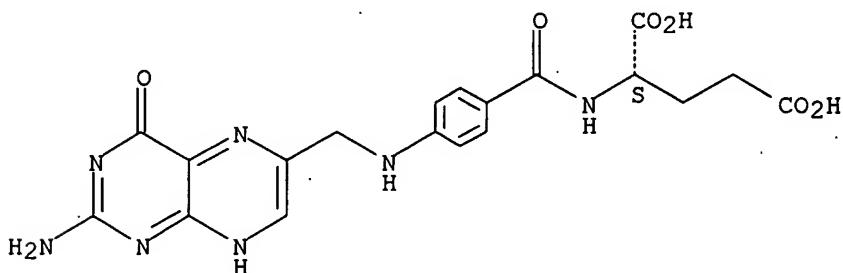
Absolute stereochemistry.



IT 59-30-3, Folic acid, biological studies
63-68-3, Methionine, biological studies 98-92-0
, Nicotinamide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compsns. with reduced hepatotoxicity)

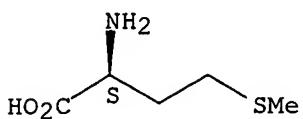
RN 59-30-3 CAPLUS
CN L-Glutamic acid, N-[4-[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

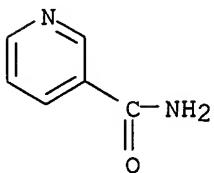


RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



L42 ANSWER 2 OF 7 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001398967 EMBASE
TITLE: **Folic acid revisited.**
AUTHOR: Hazra A.; Kumar Tripathi S.
CORPORATE SOURCE: A. Hazra, 17/2/4B Chakraberia Road (South), Calcutta 700025, India. blowfans@cal2.vsnl.net.in
SOURCE: Indian Journal of Pharmacology, (2001) Vol. 33, No. 5, pp. 322-342.
Refs: 114
ISSN: 0253-7613 CODEN: INJPD2
COUNTRY: India
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT:
029 Clinical Biochemistry
030 Pharmacology
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
025 Hematology
020 Gerontology and Geriatrics
021 Developmental Biology and Teratology
036 Health Policy, Economics and Management
005 General Pathology and Pathological Anatomy
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Nov 2001
Last Updated on STN: 30 Nov 2001
AB **Folic acid, or pteroylglutamic acid**, is a well-known water soluble vitamin of the B-complex group. It is necessary for DNA synthesis and normal erythropoiesis. Tetrahydrofolate, the active form of this vitamin, functions as a coenzyme in various metabolic reactions involving transfer of one-carbon moieties. Folate and **vitamin B(12)** metabolic pathways intersect at the conversion of homocysteine to **methionine**. Human beings cannot synthesize this vitamin and must obtain performed folate through dietary sources like green leafy vegetables, cereals, fruits, organ meats and yeast. Synthetic **folic acid** is more bioavailable than food folate. Absorption is predominantly from the upper small intestine and elimination predominantly renal, with modest **hepatic** storage. The daily requirement varies by age and is greater during pregnancy and lactation. Apart from increased demand, folate deficiency

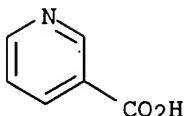
can occur in malnutrition, malabsorption, chronic hemolytic anemias, chronic alcoholism, repeated hemodialysis, and unusual dietary situations like total parenteral nutrition. The use of certain antiepileptic, antimalarial, antimicrobial and anticancer drugs may interfere with the absorption, conversion or utilization of folate leading to megaloblastic anemia. The primary therapeutic indication is in the prophylaxis and treatment of deficiency states. Pharmacological supplementation is recommended in situations like pregnancy (for preventing macrocytic anemia, occurrence or recurrence of neural tube defects, counteracting teratogenic effect of anticonvulsants, etc.), malnutrition, malabsorption and chronic hemodialysis. It may be supplemented during lactation, in infants, the elderly, alcoholics, and in renal failure patients.

Folic acid may also reduce orofacial clefting and ameliorate **methotrexate toxicity** in rheumatoid arthritis. Pharmacological dose are well-tolerated but folate supplementation alone in megaloblastic anemia primarily due to **vitamin B(12)** deficiency can worsen the neurological condition. Of late, interest in **folic acid** has grown with the realization that modest folate supplementation can prevent hyperhomocysteinemia, which is an independent graded risk factor for atherosclerotic cardiovascular disease, and is possibly beneficial in certain cancers. The recent stipulation for mandatory folate fortification of cereal products in USA and the inclusion of **folic acid** in the WHO model list of essential drugs recognize the increasing importance of folate in human nutrition. Indeed, **folic acid** has revisited with new therapeutic applications and its mysteries are still unfolding more than 7 decades after its discovery.

L42 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1953:32699 CAPLUS
DOCUMENT NUMBER: 47:32699
ORIGINAL REFERENCE NO.: 47:5557i,5558a-d
TITLE: Pharmacological studies on isonicotinic acid hydrazide
AUTHOR(S): Garattini, S.; Grassi, C.; Mantegazza, P.; Morville, V.; Tommasini, R.; Trabucchi, E.
CORPORATE SOURCE: Univ. Milan
SOURCE: Atti della Societa Lombarda di Scienze Mediche e Biologiche (1952), 7(No. Spec.), 1-19; English summary 18-19
CODEN: ASLBAG; ISSN: 0365-690X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Isonicotinic acid hydrazide (I) showed a more intense inhibiting action than streptomycin on Koch's bacilli in vitro. Vitamins B1, B2, and B6, p-aminobenzoic acid, uracil, thymine, **nicotinamide**, choline, **methionine**, **folic acid**, pantothenic acid, isonicotinic acid, and isonicotinamide were inefficient in counteracting I action. (1) p-Aminobenzoic acid hydrazide, nicotinic acid hydrazide, and isonicotinic acid amide, (2) succinic acid bishydrazide, and (3) pyrazincarboxylic acid hydrazide had, resp., (1) no, (2) some, and (3) a considerable inhibiting action on Koch's bacilli. Also in vivo, in rats, the effect of I was higher than that of streptomycin. Intravenously injected I was distributed rapidly to the various tissues, especially to liver; exchanges through the blood-tissue barrier occurred in both senses; I urinary excretion occurred within some hrs. after injection. I was rapidly destroyed in the organism (removal of both the terminal N, with formation of NH₃ and isonicotinamide, and of the whole hydrazine group with formation of isonicotinic acid). Also in vitro I was decomposed (lateral chain taken off) by slices of liver, lung, and brain and by yeasts; this action was inhibited by thiourea and p-aminobenzoic acid. Metabolisms of I and of isonicotinic acid and its amide were different from that of **nicotinamide** since the pyridine N was not alkylated. The nervous phenomena due to I

administration to animals were also investigated: the association of thiourea and p-aminobenzoic acid with I attenuated its convulsive effect, the association of pyruvic acid enhanced the resistance of animals to the toxic effects of I. The administration of I lowered the pyruvic acid level of blood in humans and animals (and of the brain of the latter), and in sound subjects caused also a drop of blood eosinophils and in guinea pigs a considerable drop of the ascorbic acid content of adrenal glands (by high I doses).

IT 59-67-6, Nicotinic acid
(hydrazides, bacteriostatic action on tubercle bacilli)
RN 59-67-6 CAPLUS
CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



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ACCESSION NUMBER: 2004257294 EMBASE

TITLE: The effect of fibrates and other lipid-lowering drugs on plasma homocysteine levels.

AUTHOR: Dierkes J.; Westphal S.; Luley C.

CORPORATE SOURCE: Dr. J. Dierkes, Inst. of Clinica Chem./Biochemistry, University Hospital Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany. jutta.dierkes@medizin.uni-magdeburg.de

SOURCE: Expert Opinion on Drug Safety, (2004) Vol. 3, No. 2, pp. 101-111.
Refs: 84
ISSN: 1474-0338 CODEN: EODSA

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 003 Endocrinology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 1 Jul 2004
Last Updated on STN: 1 Jul 2004

AB Hyperlipidaemia is a major risk factor for cardiovascular disease. The drugs of choice for the treatment of hyperlipidaemia are either fibrates, in the case of hypertriglyceridaemia, or statins, in the case of hypercholesterolaemia. Recently, it has been shown that some of the most prescribed fibrates cause hyperhomocysteinaemia, which itself has been recognised as a cardiovascular risk factor. In particular, fenofibrate and bezafibrate lead to a 20 - 40% elevation of plasma levels of the atherogenic amino acid homocysteine, thereby possibly counteracting the desired cardiovascular protection. The most likely mechanism for this increase is an alteration of creatine-creatinine metabolism and changes in methyl transfer. Gemfibrozil does not increase homocysteine. Statins have no effect on the plasma homocysteine concentration. The increase of plasma homocysteine after fenofibrate can be lowered by the concurrent administration of folic acid and vitamins B(12) and B(6). Thus, patients with hypertriglyceridaemia can either be concurrently treated with fenofibrate and vitamins or with gemfibrozil. 2004 .COPYRGT. Ashley Publications Ltd.

L42 ANSWER 5 OF 7 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 97048562 EMBASE

DOCUMENT NUMBER: 1997048562

TITLE: Male rats fed methyl- and folate-deficient diets with or without niacin develop hepatic carcinomas associated with decreased tissue NAD concentrations and altered poly(ADP-ribose) polymerase activity.

AUTHOR: Henning S.M.; Swendseid M.E.; Coulson W.F.

CORPORATE SOURCE: S.M. Henning, Community Health Sciences, School of Public Health, University of California, Los Angeles, CA 90095, United States

SOURCE: Journal of Nutrition, (1997) Vol. 127, No. 1, pp. 30-36.

Refs: 26

ISSN: 0022-3166 CODEN: JONUAI

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 10 Mar 1997
Last Updated on STN: 10 Mar 1997

AB Folate is an essential cofactor in the generation of endogenous methionine, and there is evidence that folate deficiency exacerbates the effects of a diet low in choline and methionine, including alterations in poly(ADP-ribose) polymerase (PARP) activity, an enzyme associated with DNA replication and repair. Because PARP requires NAD as its substrate, we postulated that a deficiency of both folate and niacin would enhance the development of liver cancer in rats fed a diet deficient in methionine and choline. In two experiments, rats were fed choline- and folate-deficient, low methionine diets containing either 12 or 8% casein (12% MCFD, 8% MCFD) or 6% casein and 6% gelatin with niacin (MCFD) or without niacin (MCFND) and were compared with folate-supplemented controls. Liver NAD concentrations were lower in all methyl-deficient rats after 2-17 mo. At 17 mo, NAD concentrations in other tissues of rats fed these diets were also lower than in controls. Compared with control values, liver PARP activity was enhanced in rats fed the 12% MCFD diet but was lower in MCFND-fed rats following a further reduction in liver NAD concentration. These changes in PARP activity associated with lower NAD concentrations may slow DNA repair and enhance DNA damage. Only rats fed the MCFD and MCFND diets developed hepatocarcinomas after 12-17 mo. In Experiment 2, hepatocarcinomas were found in 100% of rats fed the MCFD and MCFND diets. These preliminary results indicate that folic acid deficiency enhances tumor development. Because tumors developed in 100% of the MCFD-fed rats and because tissue concentrations of NAD in these animals were also low, further studies are needed to clearly define the role of niacin in methyldeficient rats.

L42 ANSWER 6 OF 7 MEDLINE on STN

ACCESSION NUMBER: 2002462179 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12221238

TITLE: Acute valproate administration impairs methionine metabolism in rats.

AUTHOR: Ubeda Natalia; Alonso-Aperte Elena; Varela-Moreiras Gregorio

CORPORATE SOURCE: Seccion de Nutricion, Bromatologia y Dietetica, Facultad de Ciencias Experimentales y de la Salud, Universidad San Pablo CEU, Madrid, Spain.. nubeda@ceu.es

SOURCE: The Journal of nutrition, (2002 Sep) Vol. 132, No. 9, pp. 2737-42.
 Journal code: 0404243. ISSN: 0022-3166.

PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200302
 ENTRY DATE: Entered STN: 11 Sep 2002
 Last Updated on STN: 7 Feb 2003
 Entered Medline: 6 Feb 2003

AB Valproate (VPA) is a drug widely used to treat epilepsy, but it has serious adverse effects including **hepatotoxicity**, teratogenicity and antifolate activity. The mechanism underlying VPA **toxicity** is unclear although an interaction with folate and other metabolites involved in **methionine** metabolism has been suggested. The present study was undertaken to evaluate potential changes in the metabolic function of the **methionine** cycle after acute exposure to a single dose of valproate. Female Wistar rats ($n = 30$) were treated with 400 mg/kg of VPA. Different groups of six rats were killed at 1 (t_1), 3 (t_3), 6 (t_6), 9 (t_9), and 24 (t_{24}) hours after the injection. One group of rats was untreated ($n = 6$) and was considered the control group. The most pronounced effects of VPA administration were observed 1 h after drug injection. VPA induced a 56% reduction in **methionine** adenosyltransferase activity and a 54% reduction in plasma **vitamin B-6**. Increases in the **hepatic** concentration of S-adenosylhomocysteine and oxidized glutathione, and a reduction in the S-adenosylmethionine/S-adenosylhomocysteine transmethylation ratio also occurred at 1 h. All of these alterations, however, were normalized within 24 h, parallel with a decrease in serum VPA concentration. The acute effects of VPA suggest that the alterations in the **methionine** cycle could be the common mechanism underlying the **hepatotoxic**, teratogenic and antifolate effects of the drug.

L42 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2004:162309 CAPLUS
 DOCUMENT NUMBER: 140:205217
 TITLE: System for exsanguinous metabolic support of an organ or tissue
 INVENTOR(S): Brasile, Lauren
 PATENT ASSIGNEE(S): Breonics, Inc., USA
 SOURCE: U.S. Pat. Appl. Publ., 25 pp., Cont.-in-part of U.S. Ser. No. 849,618.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004038192	A1	20040226	US 2003-443452	20030522
US 6642045	B1	20031104	US 2000-547843	20000412
US 2002012988	A1	20020131	US 2001-849618	20010504
US 6582953	B2	20030624		
US 2004038193	A1	20040226	US 2003-650986	20030827
WO 2004105484	A1	20041209	WO 2004-US16085	20040521
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:	US 1999-129257P	P 19990414
	US 2000-547843	A2 20000412
	US 2001-849618	A2 20010504
	WO 2000-US9894	W 20000413
	US 2003-443452	A 20030522

AB An exsanguinous metabolic support system for maintaining an organ or tissue at a near normal metabolic rate is disclosed that employs a warm perfusion solution capable of altering the production of nitric oxide (NO) in

an organ or tissue and supporting the metabolism of the organ or tissue at normothermic temps. Perfusion with the solution of the invention can therefore be used to regulate nitric oxide production in situations where it is desirable to do so, e.g. to prevent reperfusion injury. The system also monitors parameters of the circulating perfusion solution, such as pH, temperature, osmolarity, flow rate, vascular pressure and partial pressure of respiratory gases, and nitric oxide (NO) concentration and regulates them to insure that the organ is maintained under near-physiol. conditions. Use of the system for long-term maintenance of organs for transplantation, for resuscitation and repair of organs having sustained warm ischemic damage, to treat cardiovascular disorders, to prevent reperfusion injury, as a pharmaceutical delivery system and prognosticator of post-transplantation organ function is also disclosed.

IT 59-30-3, Folic Acid, biological studies

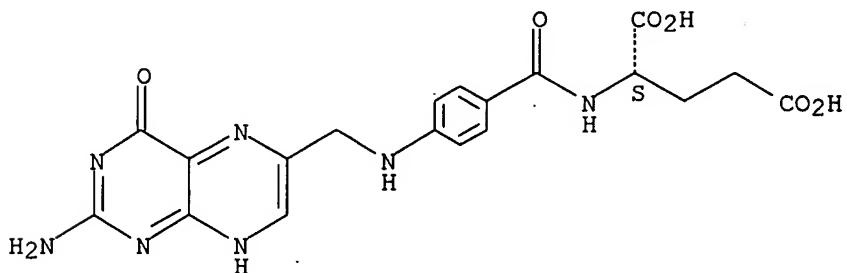
59-51-8, Methionine 59-67-6, Nicotinic Acid, biological studies 98-92-0, Niacinamide

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(system for exsanguinous metabolic support of an organ or tissue)

RN 59-30-3 CAPLUS

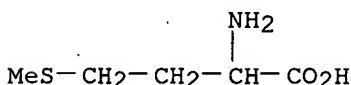
CN L-Glutamic acid, N-[4-[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



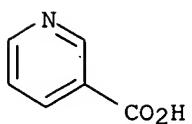
RN 59-51-8 CAPLUS

CN Methionine (9CI) (CA INDEX NAME)

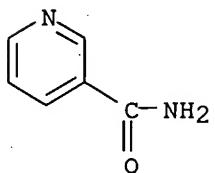


RN 59-67-6 CAPLUS

CN 3-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)



RN 98-92-0 CAPLUS
CN 3-Pyridinecarboxamide (9CI) (CA INDEX NAME)



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